

Serial No.: 09/998,058

REMARKS

I. Status Summary

Claims 1-27 and 46-53 are pending in the present U.S. patent application.

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5231-5236 (hereinafter "Diehl").

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans").

Claims 1-27 and 46-53 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter that the applicants regard as the invention.

Claims 28-45 and 54-59 are herein canceled without prejudice. Applicants hereby reserve the right to file one or more divisional applications directed to the unelected subject matter. Reconsideration of the application based on the remarks set forth below is respectfully requested.

II. General Considerations

The presently claimed subject matter pertains to a novel population of genetically diverse individuals that can be used for genetic mapping, methods for generating the disclosed population, and methods for using the disclosed population for efficient identification of genetic loci that modulate a phenotype. Also disclosed is an approach based upon a modification of basic recombinant inbred strains presently available, and as such represents an advance in the ability to use such lines for genetic mapping.

One aspect pertains to the creation of the population of genetically diverse individuals. Unlike recombinant inbred (RI) mouse lines, which are characterized by individuals that are genetically homogenous (*i.e.* each individual is homozygous for each locus/gene), the genetically diverse individuals of the present invention are derived from these homogenous RI lines and are genetically diverse themselves. Mice that make up an RI line are genetically diverse across the population (*i.e.* the RI

Serial No.: 09/998,058

strain), but are not genetically diverse individually. Each individual RIX (recombinant inbred intercross) strain thus represents individuals with a complex genetic make-up, being homozygous at some loci and heterozygous at others. This is unlike the strains disclosed in Diehl, each of which employs basic RI strains that are made up of mice that individually are homozygous at each locus and thus not encompassed by the phrase "genetically diverse" as used in the instant application. The Diehl reference cited by the Patent Office does not use genetically diverse individuals, as Diehl discloses homozygous lines of mice that across all lines are genetically diverse but are not genetically diverse within a mouse, as no mouse disclosed in Diehl is heterozygous at any locus.

III. Claim Rejection Under 35 U.S.C. § 102(b)

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl et al. (1997) Proc. Natl. Acad. Sci. USA 94:5231-5236 (hereinafter "Diehl"). The basis for this rejection is set out on pages 2-4 of the Official Action. The United States Patent and Trademark Office (hereinafter the "Patent Office") asserts that Diehl teaches a method for identifying multiple genetic loci (*Col2a1*, *Col1a1*, and *Col3a1*) that modulate a phenotype (facial clefting) in mice. According to the Patent Office, Diehl "performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse" using recombinant inbred (RI) mouse strains provided by M. Nesbitt. Official Action, page 2. The AXB and BXA RI lines are asserted to be crosses between A/J and C57BL6/J strains which were bred by intercrossing RI lines and maintained as a "renewable population of genetically diverse individuals". Diehl is also asserted to disclose the identification of loci using inbred lines using less than about 100 strains, identifying multiple genetic loci that modulate a phenotype, the modulation of a phenotype by a non-genetic factor (drug exposure), and the identification of an interaction among two or more non-genetic factors and a genetic locus.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Serial No.: 09/998,058

It is well settled that for a cited reference to qualify as prior art under 35 U.S.C. § 102, each element of the claimed invention must be disclosed within the reference. In re Bond, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986). When an alleged prior art reference does not disclose each and every element of the claimed invention, the claims cannot be rejected on the basis of anticipation. See, e.g., Atlas Powder Co. v. E. I. Du Pont de Nemours & Co., 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984); Continental Can Co. U.S.A. Inc. v. Monsanto Co., 948 F.2d 124, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991). Upon careful consideration of Diehl, applicants respectfully submit that Diehl does not disclose each and every element of claims 1-10, 15, 19-27, and 46-53. Specifically, Diehl does not disclose a "renewable population of genetically diverse individuals" as that phrase is used in the present application.

Applicants respectfully submit that the phrase "genetically diverse" has been misinterpreted by the Patent Office, and when used as it is disclosed in the specification of the instant application and described hereinabove, it is clear that the mouse lines produced by Diehl are not genetically diverse. According to the specification as filed, "a renewable population of genetically diverse individuals can comprise: (a) individuals produced by intercrossing recombinant inbred lines; (b) individuals produced by backcrossing recombinant inbred lines; (c) a cloned population of genetically diverse individuals; or (d) a panel of cell lines derived from genetically diverse individuals." The mouse lines that are disclosed in Diehl are not genetically diverse in this way. As noted above, the mouse lines disclosed in Diehl are all basic recombinant inbred lines, which do not fit the definition of "genetically diverse individuals" as used in the instant application. Briefly, unlike the recombinant inbred lines of Diehl, a "genetically diverse" individual of the instant invention is itself (i.e. individually) genetically diverse, whereas the individuals of the RI strains of Diehl are not individually genetically diverse.

Applicants respectfully submit that when considered in the context of how the phrase "genetically diverse" is being used in the present application, it becomes clear

Serial No.: 09/998,058

that the Diehl reference does not disclose a population of genetically diverse individuals. Thus, applicants respectfully submit that Diehl does not disclose each and every element of the claimed invention, and thus does not qualify as an anticipating reference under In re Bond, Hybritech, and Atlas Powder. Accordingly, applicants respectfully request that the rejection of claims 1-10, 15, 19-27, and 46-53 under 35 U.S.C. § 102(b) as being anticipated by Diehl be withdrawn. Applicants further respectfully submit that claims 1-10, 15, 19-27, and 46-53 are in condition for allowance, and respectfully request a Notice of Allowance to that effect.

IV. Claim Rejection Under 35 U.S.C. § 103

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans et al. (1986) J. Immunol 137:2355-2360 (hereinafter "Dindzans"). The basis for this rejection can be found in the Official Action at pages 4-7. The Patent Office asserts that Diehl teaches a method for identifying multiple genetic loci. The Patent Office concedes, however, that Diehl does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines. The Patent Office asserts that Dindzans teaches the production of RI lines from multiple parent strains. The Patent Office thus contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype of Diehl so as to have included the diverse population of non-recombinant, parent lines derived from at least 3, 4, or 8 non-recombinant parent lines.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Preliminarily, applicants note that the U.S. Court of Appeals for the Federal Circuit (C.A.F.C.) has set forth in Environmental Design Ltd. v. Union Oil Co., 713 F.2d 693 (Fed. Cir. 1983), cert. denied, 464 U.S. 1043 (1984), that the factual determinations to be made, as well as the evidence to consider, in making an obviousness determination under §103 include:

- a) the scope and content of the prior art;

Serial No.: 09/998,058

- b) the differences between the prior art and the claimed invention;
- c) the level of ordinary skill in the pertinent art; and
- d) additional evidence, which may serve as indicia of non-obviousness.

All relevant evidence on each of these four dispositive issues must be fully considered and evaluated to determine whether the claimed invention would have been obvious. Additionally, it is well known that for an obviousness-type rejection to stand, the cited document or combination must disclose all aspects of the claimed invention; contain a suggestion to modify the cited document(s) to arrive at the claimed invention; and there must be a reasonable chance of success.

In Hodosh v. Block Drug Co., 786 F.2d 1136 (Fed. Cir. 1986), the U.S. Court of Appeals for the Federal Circuit set forth what is described as the "tenets of patent law that must be adhered to when applying §103", Id. at 1143, n.5. Those tenets set out in Hodosh are:

- a) the claimed invention must be considered as a whole;
- b) the references must be considered as a whole and suggest the desirability and thus obviousness of making the combination;
- c) the references must be reviewed without benefit of hindsight vision afforded by the claimed invention; and
- d) "ought to be tried" is not the standard with which obviousness is determined.

The claims subject to the present rejection depend from claims 1 and 2. Claim 1 recites a method for identifying a genetic locus that modulates a phenotype comprising:

- (a) providing a renewable population of genetically diverse individuals; and
- (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified.

Claim 2 depends from claim 1, and recites that the renewable population of genetically diverse individuals comprises:

- (a) individuals produced by intercrossing recombinant inbred lines;
- (b) individuals produced by backcrossing recombinant inbred lines;

Serial No.: 09/998,058

- (c) a cloned population of genetically diverse individuals; or
- (d) a panel of cell lines derived from genetically diverse individuals.

Claims 11-14 and 16-18 then recite that the recombinant inbred lines comprise recombinant inbred lines derived from at least 3 (claims 11 and 16), 4 (claims 12 and 17), or 8 (claims 13 and 18) non-recombinant parent lines. Claim 14 depends from claim 11, and recites that the at least three non-recombinant parent lines comprise one or more non-recombinant parent lines selected from the group consisting of mouse lines C57BL/6, BALB/c, C3H, A, 129, and DBA/2.

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans. The Patent Office asserts that Diehl teaches a method for identifying multiple genetic loci. The Patent Office concedes, however, that Diehl does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines. The Patent Office contends that this defect is cured by Dindzans, which is asserted to teach the production of RI lines from multiple parent strains.

The above-noted deficiencies of the Diehl reference are incorporated here by reference. Additionally, contrary to the Patent Office's contentions, applicants respectfully submit that the Dindzans reference does not disclose the production of RI lines from multiple (*i.e.* 3 or more) non-recombinant parental lines. As recited on page 2356 of Dindzans, "RI strains were derived by inbreeding mice from the F₂ generation of the cross between A/J (A) and C57BL/6J (B) mice...". As a result, applicants respectfully point out that Dindzans only used 2 non-recombinant parental lines: A/J and C57BL/6J, not the at least 3 recited in claims 11-14 and 16-18 of the instant application. As such, applicants respectfully submit that the combination of Diehl and Dindzans does not disclose each and every element of the claimed invention, and thus, a prima facie case of obviousness has not been established.

Furthermore, the Dindzans reference cited by the Patent Office refers to more related lines derived from the same two parental lines (*i.e.* more AXB lines from the same two parental strains), not to using more parental lines to derive RI lines containing greater than two parental lines. Up to this point, the art has strived to simplify the analysis to only two possible alleles at any locus (gene) as in the case of

Serial No.: 09/998,058

an RI derived from two parents. Applicants respectfully submit that having more than two parents to derive an RI can introduce more than two alleles, and thus, would not have been obvious to one of ordinary skill in the art attempting to simplify the system.

Applicants further respectfully submit that there is no suggestion in Dindzans to employ at least 3 non-recombinant parental lines. The Patent Office appears to assert that "parental strain diversity" and "having a 'unique assortment of parental genes that are homozygous at every locus'" are important considerations taught by Dindzans. Official Action, page 7. Dindzans employed two parental strains "representing extremes in disease" (page 2357, Discussion), and thus does not suggest that generating "parental strain diversity" requires more than 2 parental strains. Additionally, "having a 'unique assortment of parental genes that are homozygous at every locus'" teaches away from the present invention, in which the genetically diverse individuals are purposefully not homozygous at every locus.

As a result, applicants respectfully submit that the combination of Diehl and Dindzans does not support the current rejection. Accordingly, applicants respectfully request that the rejection of claims 11-14 and 16-18 under 35 § 103(a) be withdrawn and the claims be allowed at this time.

IV. Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-27 and 46-53 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter that the applicants regard as the invention. According to the Patent Office, the phrase "renewable population" is indefinite in that it is unclear whether the phrase is intended to refer to a "perpetuated living cell line, a freezer stock, desiccated sample, etc."

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

It is respectfully submitted that the specification must be viewed from the perspective of the skilled artisan. According to the Court of Appeal for the Federal Circuit (hereinafter the "Federal Circuit"), "the definiteness inquiry focuses on whether

Serial No.: 09/998,058

those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification". See Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576 (Fed. Cir. 1986). Furthermore, claim language need only "reasonably apprise those skilled in the art" as to the scope of the claim, and be "as precise as the subject matter permits". See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). And finally, the Federal Circuit has stated: "if the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more". Id.

Applicants respectfully submit that the specification as filed reasonably apprises one of ordinary skill in the art as to the scope of the rejected claims. According to the specification, the phrase "renewable population of genetically diverse individuals" refers to a population that can be faithfully regenerated and comprises a limited repertoire of possible genotypes, although individuals within the population are genetically diverse. The specification defines the term "individual" as an organism or a cell derived therefrom. The population can comprise any diploid, tetraploid, or polyploid individual. In exemplary embodiments, an individual of the renewable population is an animal or a plant. In one embodiment, an animal is a mammal, in another embodiment a rodent, and in yet another embodiment a mouse.

Applicants respectfully submit that given the definition of "renewable population of genetically diverse individuals" and "individual" in the specification as filed, the metes and bounds would be clear to one of ordinary skill. Accordingly, applicants respectfully submit that the rejection of claims 1-27 and 46-53 under 35 U.S.C. § 112, second paragraph, has been addressed, and that these claims are now in condition for allowance. Applicants respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully

Serial No.: 09/998,058

requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: June 26, 2003

By: Arls A. Taylor, Jr.

Arls A. Taylor, Jr.
Registration No. 39,395

421/34/2

AAT/CP/ptw

Customer No. Bar Code:



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Enclosures: